Report on the Deliberation Results

May 29, 2024
Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Brand Name	Ezharmia Tablets 50 mg Ezharmia Tablets 100 mg
Non-proprietary Name	Valemetostat Tosilate (JAN*)
Applicant	Daiichi Sankyo Company, Limited
Date of Application	January 31, 2024

Results of Deliberation

In its meeting held on May 24, 2024, the Second Committee on New Drugs concluded that the partial change application for the product may be approved and that this result should be presented to the Pharmaceutical Affairs Council.

The re-examination period is the remainder of the re-examination period for the initial approval (until September 25, 2032).

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Given the extremely limited number of Japanese patients participated in clinical studies, the applicant is required to conduct a drug use-results survey involving all Japanese patients treated with the product after the market launch until data are gathered from a certain number of patients to understand the characteristics of patients using the product, and to promptly collect safety and efficacy data so that necessary measures are taken to ensure proper use of the product.

**Japanese Accepted Name (modified INN)*

Review Report

April 25, 2024
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Ezharmia Tablets 50 mg Ezharmia Tablets 100 mg
Non-proprietary Name	Valemetostat Tosilate
Applicant	Daiichi Sankyo Company, Limited
Date of Application	January 31, 2024
Dosage Form/Strength	Tablets: Each tablet contains 67.6 mg or 135 mg of Valemetostat Tosilate (50 mg or 100 mg of valemetostat).
Application Classification	Prescription drug, (4) Drug with a new indication
Items Warranting Special Mention	SAKIGAKE designation drug (SAKIGAKE Drug Designation No. 1 of 2019 [*31 yaku*]; PSEHB/PED Notification No. 0408-1 dated April 8, 2019, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)
Reviewing Office	Office of New Drug V

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has a certain efficacy in the treatment of patients with relapsed or refractory peripheral T-cell lymphoma, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indications and dosage and administration shown below, with the following approval conditions. Myelosuppression, infections, and secondary malignant tumor are subject to further investigation through post-marketing surveillance.

Indications

Relapsed or refractory adult T-cell leukemia-lymphoma

Relapsed or refractory peripheral T-cell lymphoma

(Underline denotes additions.)

Dosage and Administration

The usual adult dosage is 200 mg of valemetostat orally administered once daily in the fasted state. The dose may be reduced according to the patient's condition.

(No change)

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Given the extremely limited number of Japanese patients participated in clinical studies, the applicant is required to conduct a drug use-results survey involving all Japanese patients treated with the product after the market launch until data are gathered from a certain number of patients to understand the characteristics of patients using the product, and to promptly collect safety and efficacy data so that necessary measures are taken to ensure proper use of the product.

Attachment

Review Report (1)

March 28, 2024

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

Brand Name	Ezharmia Tablets 50 mg Ezharmia Tablets 100 mg
Non-proprietary Name	Valemetostat Tosilate
Applicant	Daiichi Sankyo Company, Limited
Date of Application	January 31, 2024
Dosage Form/Strength	Tablets: Each tablet contains 67.6 mg or 135 mg of Valemetostat Tosilate (50 mg or 100 mg of valemetostat).

Proposed Indications

Relapsed or refractory adult T-cell leukemia-lymphoma
Relapsed or refractory peripheral T-cell lymphoma

(Underline denotes additions.)

Proposed Dosage and Administration

The usual adult dosage is 200 mg of valemetostat orally administered once daily in the fasted state. The dose may be reduced according to the patient's condition.

(No change)

Table of Contents

List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

1.1 Outline of the proposed product

Valemetostat Tosilate (hereinafter referred to as "valemetostat") is a low-molecular compound with inhibitory effect against the enhancer of zeste homolog 1 and 2 (EZH1/2) discovered by the applicant. Valemetostat is expected to suppress tumor growth by inhibiting methylation activity of EZH1/2 and inducing apoptosis.

In Japan, valemetostat was approved for the indication of "relapsed or refractory adult T-cell leukemia-lymphoma" in September 2022.

1.2 Development history, etc.

For clinical development targeting peripheral T-cell lymphoma (PTCL), the applicant initiated a global phase II study (Study DS3201-A-U202 [Study U202]) in patients with relapsed or refractory PTCL in June 2021.

As of January 2024, valemetostat has not been approved for the indication of relapsed or refractory PTCL in any country or region.

In Japan, the applicant started patient enrollment in the Study U202 in June 2021.

Recently, an application for partial change approval for valemetostat has been submitted to add an indication of relapsed or refractory PTCL with the results of Study U202 as pivotal data.

Valemetostat was designated as a SAKIGAKE designation drug with the intended indication of "relapsed or refractory peripheral T-cell lymphoma" in April 2019 (SAKIGAKE Drug Designation No. 1 of 2019 [*31 yaku*]).

2. Quality and Outline of the Review Conducted by PMDA

The present application is for a new indication, and no data related to quality are submitted.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

3.1 Primary pharmacodynamics

3.1.1 Growth inhibitory effect against human T-cell tumor cell lines

3.1.1.1 *In vitro* (CTD 4.2.1.1-1)

The growth inhibitory effect of valemetostat and tazemetostat (EZH2 inhibitor) against human T-cell tumor MTA cell line[1)] and human T-cell lymphoma DL-40 cell line was investigated using an amount of viable cell-derived adenosine triphosphate (ATP) as an indicator. Table 1 shows 50% growth inhibitory concentrations (GI_{50}) of valemetostat and tazemetostat.

1) Cell line with both lymphocytic leukemia (natural killer [NK]-cell and T-cell) phenotypes

Table 1. Growth inhibitory effect of valemetostat and tazemetostat against MTA and DL-40 cell lines

Cell line	GI_{50} (nmol/L)	
	Valemetostat	Tazemetostat
MTA	0.776	2.61
DL-40	1.22	6.20

n = 1

3.R Outline of the review conducted by PMDA

On the basis of the data submitted, PMDA has concluded that the applicant's explanation about non-clinical pharmacology of valemetostat is acceptable except for the following.

3.R.1 Efficacy against PTCL

The applicant's explanation about the efficacy of valemetostat against PTCL:

In view of the following findings, valemetostat is expected to have efficacy against PTCL, a type of T-cell tumor:

- Valemetostat binds to both EZH1 and EZH2, inhibits their methylation activities, thereby inducing apoptosis of various hematopoietic malignancies including adult T-cell leukemia/lymphoma (ATL) (see the initial Review Report).
- Although there are no non-clinical study results on the growth inhibitory effect of valemetostat against human PTCL cell lines, valemetostat inhibited the growth of the human T-cell tumor cell line [see Section 3.1.1.1].

PMDA's review:

The applicant's explanation is generally acceptable. However, the degree of the contribution of EZH1 or EZH2 to PTCL proliferation and factors affected by valemetostat's inhibitory effect on methylation in PTCL remain largely unexplained. A direct association between the valemetostat's inhibitory effects on methylation activity and tumor-growth inhibition also remains unclear. Information about factors affecting the efficacy of valemetostat in patients with PTCL may be critical in the prediction of valemetostat's efficacy in clinical use and for the identification of eligible patients. The applicant therefore needs to continue information collection and appropriately update healthcare professionals with new findings whenever available.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

Although the present application is for a new indication, the data related to non-clinical pharmacokinetics had been evaluated during the review process for the initial approval. Thus, no new data have been submitted.

5. Toxicity and Outline of the Review Conducted by PMDA

The present application is for a new indication, and no data related to toxicity are submitted.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

The applicant submitted data on the valemetostat measurement method as data related to biopharmaceutic studies and associated analytical methods.

6.1 Clinical pharmacology

The pharmacokinetics (PK) of valemetostat in patients with cancer was investigated after the administration of valemetostat alone. A drug-drug interaction (DDI) study was conducted to investigate the effect of valemetostat on the PK of midazolam or digoxin (DDI cohort in Study DS3201-A-J101 [Study J101]). While the assessment for the initial approval based on the preliminary analysis results, the final analysis results were submitted for the present partial change application.[2)]

6.1.1 Global phase I study (CTD 5.3.3.2-1, dose escalation, dose expansion, and DDI cohort in Study J101, ongoing since March 2016 [data cut-off on December 31, 2022])

An open-label, uncontrolled study was conducted in 91 patients with relapsed or refractory PTCL, etc. (90 patients included in the PK analysis) to investigate the PK of valemetostat. Valemetostat was orally administered in the fasted state QD at 150, 200, 250, and 300 mg in the dose escalation part and at 200 mg in the dose expansion part.

Table 2 shows PK parameters of valemetostat in patients with PTCL in the dose expansion part.

Table 2. PK parameters of valemetostat in patients with PTCL in the dose expansion part

Day of measurement (Day)	n	C_{max} (ng/mL)	t_{max}*1 (h)	AUC_{tau} (ng•h/mL)	$t_{1/2}$ (h)
1	53	1,560 (125.3)	3.92 (0.17, 27.80)	10,800 (137.6)*2	7.89 (28.0)*3
15	46	1,620 (85.1)	2.23 (0.00, 5.95)	12,400 (70.1)*4	10.2 (30.5)*5

Geometric mean (geometric coefficient of variation, %); *1 Median (minimum, maximum); *2 n = 45; *3 n = 31; *4 n = 39; *5 n = 27

In the DDI cohort of Study J101, an open-label, uncontrolled study was conducted in 24 patients with relapsed or refractory non-Hodgkin lymphoma (NHL) (15-16 patients included in the PK analysis) to investigate the effect of valemetostat on the PK of midazolam (cytochrome P-450 [CYP] 3A isoform substrate) or digoxin (P-glycoprotein [P-gp] substrate). In this study, midazolam 2 mg and digoxin 0.25 mg were orally administered 4 days before the first dose of valemetostat and Day 15 in Cycle 1, and valemetostat 200 mg was orally administered QD from Days 1 to 28.

Table 3 shows the geometric mean ratio of exposure to midazolam or digoxin after concomitant use with valemetostat to that after the administration of valemetostat alone.

The applicant's explanation:
The final analysis showed similar results to that of the preliminary analysis produced for the initial approval, the cautionary advice in the current package insert against the concomitant use of valemetostat with a P-gp substrate remains valid. The concomitant use with a CYP3A substrate, for which is no cautionary advice is given in the current package insert, no additional actions are needed.

2) At the initial approval of valemetostat, the final analysis results in the DDI cohort of Study J101 were not available, but all patients completed the DDI evaluation period, and the preliminary analysis was conducted for evaluation (for the data fixed on [redacted], 20[redacted], see the initial Review Report). The final analysis included data on drug concentrations in samples additionally submitted by the study site for PK evaluation (samples from 1 subject including 3 for midazolam measurement and 2 for digoxin measurement). For the present application, the results were submitted as evaluation data.

Table 3. Effect of valemetostat on PK of midazolam or digoxin

Analyte	n	Geometric mean ratio of C_{max} [90% CI]		Geometric mean ratio of AUC_{last} [90% CI]	
		Final analysis	Preliminary analysis	Final analysis	Preliminary analysis
Midazolam	15	0.966 [0.769, 1.213]	0.926 [0.726, 1.183]	0.874 [0.745, 1.025]	0.861 [0.732, 1.013]
Digoxin	16	1.298 [1.074, 1.568]	1.298 [1.074, 1.568]	1.270 [1.061, 1.520]	1.271 [1.062, 1.522]

6.1.2 Relationships between exposure and efficacy or safety

6.1.2.1 Relationship between exposure and efficacy

Based on data from the global phase II study (Study U202), an association between exposure to unbound valemetostat[3)] (mean concentration until the time of the best overall response or the final dose, whichever came earlier) and the response rate was investigated. No clear association was observed between exposure to unbound valemetostat and the response rate based on independent central assessment.

6.1.2.2 Relationship between exposure and safety

Based on data from the Japanese phase II study (Study DS3201-A-J201 [Study J201]), global phase I study (Study J101), and global phase II study (Study U202), associations between exposure to unbound valemetostat[3)] (mean concentration until onset of an adverse event or the final dose, whichever came earlier) and (a) Grade ≥3 platelet count decreased, (b) Grade ≥3 neutrophil count decreased, (c) Grade ≥3 anaemia, (d) adverse events leading to dose reduction, (e) adverse events leading to interruption, and (f) Grade ≥3 adverse events were investigated. The results revealed, with increasing exposure to unbound valemetostat, decreased incidences of (a) Grade ≥3 platelet count, and a tendency toward increasing incidences of (c) Grade ≥3 anaemia, (e) adverse events leading to interruption, and (f) Grade ≥3 adverse events. However, no clear association was observed between exposure to unbound valemetostat and the incidence of (b) Grade ≥3 neutrophil count decreased or (d) adverse events leading to dose reduction.

6.R Outline of the review conducted by PMDA

On the basis of the data submitted, PMDA has concluded that the applicant's explanation about clinical pharmacology of valemetostat is acceptable.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted efficacy and safety evaluation data in the form of results from studies presented in Table 4.

3) Estimated by the population pharmacokinetics (PPK) analysis.

Table 4. List of clinical studies for efficacy and safety

Data category	Region	Study ID	Phase	Study population	Number of enrollments	Dosage regimen	Major endpoints
Evaluation	Global	J101	I	Dose escalation part: Patients with relapsed or refractory NHL Dose expansion part: Patients with relapsed or refractory ATL (ATL cohort) and patients with PTCL (PTCL cohort) DDI cohort: Patients with relapsed or refractory NHL	(a) 25 (b) ATL cohort 12 PTCL cohort 54 (c) 24	(a) Dose escalation part: Oral valemetostat 150-300 mg QD (in the fasted state) (b) Dose expansion part: Oral valemetostat 200 mg QD (in the fasted state) (c) DDI cohort: Oral valemetostat 200 mg with midazolam or digoxin (in the fasted state)	Safety PK
	Global	U202	II	Cohort 1 (PTCL cohort): Patients with relapsed or refractory PTCL Cohort 2 (ATL cohort): Patients with relapsed or refractory ATL	Cohort 1: 133 Cohort 2: 22	Oral valemetostat 200 mg QD (in the fasted state)	Efficacy Safety

Each clinical study is summarized below. The main adverse events other than death observed in each clinical study are described in Section "7.2 Adverse events, etc. observed in clinical studies," and results of clinical studies for PK in Section "6.1 Clinical pharmacology."

7.1 Evaluation data

7.1.1 Clinical studies

7.1.1.1 Global phase I study (CTD 5.3.3.2-1, Study J101, ongoing since March 2016 [data cut-off on December 31, 2022])

An open-label, uncontrolled study was conducted in patients with relapsed or refractory NHL (maximum target sample size, 27 subjects in the dose escalation part) and patients with relapsed or refractory ATL or PTCL (maximum target sample size, 10 subjects in the ATL cohort, 50 subjects in the PTCL cohort in the dose expansion part) to investigate the safety of valemetostat at 19 study sites in the 2 countries, Japan and the US.[4] During the study, the data available up to the cut-off on November 2, 2020 had already been assessed for the initial approval (see the initial Review Report).

Valemetostat was orally administered in the fasted state[5] QD at 150, 200, 250, and 300 mg in the dose escalation part and then 200 mg in the dose expansion part, and the treatment was continued until the criteria for treatment discontinuation were met.

All of 91 patients enrolled in the study (25 in the dose escalation part [7 in the 150 mg cohort, 9 in the 200 mg cohort, 7 in the 250 mg cohort, 2 in the 300 mg cohort], 66 in the dose expansion part [12 in the ATL cohort, 54 in the PTCL cohort]) received valemetostat and 90 patients except 1 patient in the dose

[4] The outline of the DDI cohort is omitted in this section [see Section 6.1.1].
[5] Administered ≥1 hour before or ≥2 hours after a meal.

expansion part[6] were included in the safety analysis population (including 46 Japanese patients). Of the safety analysis population, 25 patients in the dose escalation part were included in the dose limiting toxicity (DLT) evaluation.

During the 28-day DLT evaluation period after the start of valemetostat treatment, DLT was observed in 1 of 9 patients in the 200 mg cohort (Grade 4 platelet count decreased in 1 patient) and 2 of 2 patients in the 300 mg cohort (Grade 3 anaemia/Grade 4 platelet counts decreased in 1 patient and Grade 4 platelet count decreased in 1 patient), and valemetostat 200 mg was specified as the recommended dose.

The safely analysis revealed no deaths in the dose escalation part during the valemetostat treatment or within 35 days after the end of the treatment. However, deaths occurred during the dose expansion part in 2 of 65 patients (3.1%), both owing to disease progression (no deaths in the Japanese patients). Deaths occurred in 4 of 24 patients (16.7%) in the DDI cohort[7] during the valemetostat treatment or within 35 days after the end of the treatment, and the cause of the death other than disease progression (3 patients) was acute respiratory failure/haemophagocytic lymphohistiocytosis in 1 patient, for which a causal relationship to valemetostat was ruled out.

7.1.1.2 Global phase II study (CTD 5.3.5.2-1, Study U202, ongoing since June 2021 [data cut-off on May 5, 2023])

An open-label, uncontrolled study was conducted in patients with relapsed or refractory PTCL or ATL (target sample size, 128 subjects in the PTCL cohort,[8] 20 subjects in the ATL cohort) to investigate the efficacy and safety of valemetostat at 53 study sites in 12 countries including Japan.[9]

Valemetostat was orally administered in the fasted state[5] QD at 200 mg, and the treatment was continued until the criteria for treatment discontinuation were met.

In the PTCL cohort, all 133 patients enrolled received valemetostat and were included in the safety analysis population (including 16 Japanese patients). Of these, 119 patients were included in the efficacy analysis population (including 15 Japanese patients) and the remaining 14 patients were excluded.[10]

Table 5 shows results on the response rates based central assessment according to the criteria for response assessment in the Lugano classification (*J Clin Oncol.* 2014;2:3059-68)[11] in the overall and Japanese populations, the primary endpoint.

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6) The patient received valemetostat 200 mg but was excluded from the analysis population owing to GCP violation (examination performed before informed consent).

7) No Japanese patients were included in the DDI cohort.

8) The sample size of 115 was calculated as a size that would provide ≥90% power to detect a response rate with the lower limit of 95% confidence interval (CI) greater than 27%, the threshold response rate, on the assumption that the expected response rate was 42%. The threshold response rate was defined based on clinical study results of drugs for treatment of relapsed or refractory PTCL (belinostat [unapproved in Japan], romidepsin, and pralatrexate; their response rate was 25.8%, 26.2%, and 26.6%, respectively) (*J Clin Oncol.* 2015;33:2492-9, *J. Clin Oncol.* 2012;30:631-6, *J Clin Oncol.* 2011;29:1182-9). Given this, the target sample size was determined as 128 in consideration of the possibility that 10% of the enrolled subjects could have histologically ineligible PTCL based on central pathological assessment.

9) The outline of the ATL cohort includes safety information only.

10) Patients for whom central pathological assessment was not feasible or those whose PTCL was found ineligible based on central pathological assessment

11) The primary evaluation was the effect assessment based on CT images.

Table 5. Best overall response and response rate
(central assessment, efficacy analysis population, data cut-off on May 5, 2023)

Best overall response	Number of patients (%)	
	Overall population n = 119	Japanese population n = 15
CR	17 (14.3)	3 (20.0)
PR	35 (29.4)	5 (33.3)
SD	21 (17.6)	1 (6.7)
NED[*1]	1 (0.8)	0
PD	27 (22.7)	5 (33.3)
NA	18 (15.1)	1 (6.7)
Response (CR or PR) (response rate [95% CI][*2] [%])	52 (43.7 [34.6, 53.1])	8 (53.3 [26.6, 78.7])

*[1] The centrally-assessed result in a patient in whom the treatment effect assessment based on computed tomography (CT) images according to the Lugano classification was not feasible
*[2] Clopper-Pearson method

The safety analysis revealed deaths in 15 of 133 patients (11.3%) in the PTCL cohort during the valemetostat treatment or within 30 days after the end of the treatment (no deaths in the Japanese patients). The causes of deaths other than disease progression (10 patients) were pneumonia bacterial, haemophagocytic lymphohistiocytosis, hepatic failure, pseudomonal sepsis, and pneumonia fungal in 1 patient each. A causal relationship to valemetostat was ruled out for all these events. In the ATL cohort,[12)] deaths occurred in 5 of 22 patients (22.7%) during the same period as above. The causes of deaths other than disease progression (3 patients) were unknown[13)] and bronchopulmonary aspergillosis in 1 patient each. A causal relationship to valemetostat was ruled out for bronchopulmonary aspergillosis (the causes of deaths in 2 Japanese patients were unknown and bronchopulmonary aspergillosis in 1 patient each).

7.R Outline of the review conducted by PMDA

7.R.1 Data for review

In the evaluation data submitted, the PTCL cohort in the global phase II study in patients with relapsed or refractory PTCL (Study U202) is considered to provide the pivotal data for efficacy and safety evaluation of valemetostat. PMDA, therefore, decided to review focusing on this study.

PMDA also decided to assess the efficacy in Japanese patients in a systematic manner based on data in Study U202, etc., according to "Basic Principles on Global Clinical Trials" (PFSB/ELD Notification No. 0928010, dated September 28, 2007), "Partial Revision of Basic Principles on Global Clinical Trials (Reference Cases)" (Administrative Notice dated December 10, 2021), and "Guideline for General Principles for Planning and Design of Multi-regional Clinical Trials" (PSEHB/PED Notification No. 0612-1 dated June 12, 2018).

7.R.2 Efficacy

Based on the following review, PMDA has concluded that valemetostat had demonstrated a certain degree of efficacy in patients with relapsed or refractory PTCL.

12) In the ATL cohort, 8 Japanese patients were included.
13) 7[redacted]-year old Japanese male. He contracted COVID-19 infection (Grade 1) on Day 25 of Cycle 15 of valemetostat treatment and discontinued the treatment. Six days after onset, COVID-19 infection progressed to Grade 3, and the patient was hospitalized for treatment. Grade 4 cerebral infarction occurred 26 days after the onset of COVID-19 infection, and he died of cerebral infarction and disease progression. The cerebral infarction was considered unrelated to valemetostat.

7.R.2.1 Efficacy endpoints and evaluation results

In the PTCL cohort in Study U202, the primary endpoint, i.e., the lower limit of 95% confidence interval (CI) of the response rate based on central assessment according to the criteria for response assessment in the Lugano classification, exceeded the pre-determined threshold response rate (27%) [see Section 7.1.1.2].

Figure 1 shows the maximum percent change in total tumor size (sum of bidimensional products) of the nodal/extranodal target lesions in patients with evaluable lesions at baseline in the PTCL cohort in Study U202. The secondary endpoint, i.e., the median duration of the centrally-assessed response [95% CI] (months), was 11.9 [7.8, unevaluable].

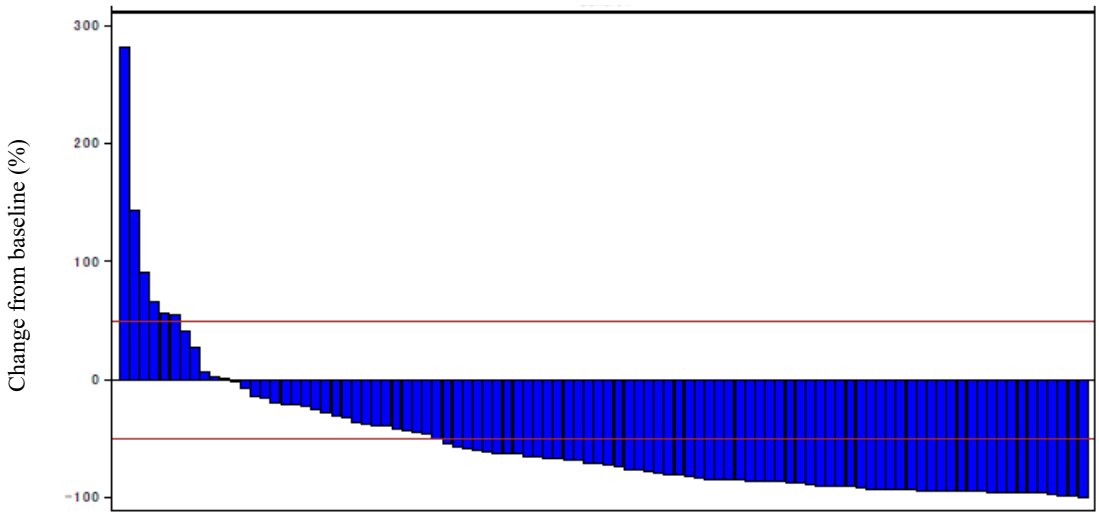

Figure 1. Maximum percent change in total tumor size (sum of the products of the diameters) of nodal/extranodal target lesions
(Lugano classification, efficacy analysis population, central assessment)

The response rate [95% CI] (%) based on central assessment according to the criteria for response assessment in the Lugano classification in the Japanese subgroup in the PTCL cohort in Study U202 was 53.3 [26.6, 78.7], which did not clearly differ from the result in the overall population [see Section 7.1.1.2].

The applicant's explanation about the response rate, the primary endpoint in Study U202:
Patients with relapsed or refractory PTCL have poor prognosis, and there is no established standard therapy that extends overall survival (OS). Given such circumstances, it is of clinical significance that these patients respond to valemetostat, which leads to the reduction of tumor volume and improvement in clinical symptoms.

PMDA's review:
The applicant's explanation about the efficacy endpoint is understandable. Based on the above results, valemetostat demonstrated a certain degree of efficacy in patients with relapsed or refractory PTCL.

7.R.3 Safety [for adverse events, see Section "7.2 Adverse events, etc. observed in clinical studies"]

PMDA's view:

Based on the following review, treatment with valemetostat in patients with relapsed or refractory PTCL requires special attention to the adverse events (myelosuppression, infections, and secondary malignant tumor), which were identified as such in the previous review for the approved indication (see the initial Review Report). These events are of attention during the use of valemetostat.

Despite the above adverse events of attention in the treatment, valemetostat will be tolerable when appropriate measures, i.e., monitoring and managing of adverse events, the interruption, dose reduction, and discontinuation of valemetostat, are taken by physicians with adequate knowledge and experience in treatment of hematopoietic malignancy. However, post-marketing safety information should be further collected in view of extremely limited treatment experience with valemetostat [see Section 7.R.6].

7.R.3.1 Safety profile of valemetostat and difference in safety between Japanese and non-Japanese patients

The applicant's explanation about the safety profile of valemetostat based on the safety data of patients with PTCL treated with valemetostat 200 mg, the proposed dosage regimen, in Studies J101 and U202:

Table 6 outlines safety in patients with PTCL treated with valemetostat 200 mg in Studies J101 and U202.

Table 6. Outline of safety (Studies J101 and U202)

	Number of patients (%)			
	Study J101 (patients with PTCL*)	Study U202 (PTCL cohort)		
	n = 55	Overall population n = 133	Japanese population n = 16	Non-Japanese population n = 117
All adverse events	55 (100)	128 (96.2)	15 (93.8)	113 (96.6)
Grade ≥3 adverse events	38 (69.1)	77 (57.9)	11 (68.8)	66 (56.4)
Adverse events resulting in death	0	15 (11.3)	0	15 (12.8)
Serious adverse events	28 (50.9)	53 (39.8)	4 (25.0)	49 (41.9)
Adverse events leading to treatment discontinuation	6 (10.9)	13 (9.8)	0	13 (11.1)
Adverse events leading to interruption	29 (52.7)	66 (49.6)	9 (56.3)	57 (48.7)
Adverse events leading to dose reduction	4 (7.3)	21 (15.8)	3 (18.8)	18 (15.4)

* Patients with PTCL treated with valemetostat 200 mg in the dose escalation part and dose expansion part

Table 7 shows all-grade adverse events with an incidence of ≥20% in either patients with PTCL treated with valemetostat 200 mg in Study J101 or the PTCL cohort in Study U202.[14)]

[14)] The following respective adverse events were counted according to the preferred terms (PTs) of the Medical Dictionary for Regulatory Activities (MedDRA) specified.
- Platelet count decreased: "Thrombocytopenia" and "Platelet count decreased"
- Anaemia: "Anaemia", "Haemoglobin decreased," and "Red blood cell count decreased"
- White blood cell count decreased: "Leukopenia" and "White blood cell count decreased"
- Neutrophil count decreased: "Neutropenia" and "Neutrophil count decreased"
- Lymphocyte count decreased: "Lymphopenia" and "Lymphocyte count decreased"

Table 7. Adverse events with an incidence of ≥20% in either study (Studies J101 and U202)

SOC PT (MedDRA/J ver.26.0)	Number of patients (%)			
	Study J101 (patients with PTCL*) n = 55		Study U202 (PTCL cohort) n = 133	
	All grades	Grade ≥3	All grades	Grade ≥3
All adverse events	55 (100)	38 (69.1)	128 (96.2)	77 (57.9)
Infections and infestations				
COVID-19	5 (9.1)	0	28 (21.1)	4 (3.0)
Nervous system disorders				
Dysgeusia	24 (43.6)	0	38 (28.6)	0
Gastrointestinal disorders				
Diarrhoea	15 (27.3)	1 (1.8)	39 (29.3)	5 (3.8)
Nausea	15 (27.3)	0	23 (17.3)	1 (0.8)
General disorders and administration site conditions				
Fatigue	11 (20.0)	2 (3.6)	19 (14.3)	2 (1.5)
Investigations				
Platelet count decreased	30 (54.5)	13 (23.6)	66 (49.6)	31 (23.3)
Anaemia	22 (40.0)	10 (18.2)	47 (35.3)	25 (18.8)
Neutrophil count decreased	15 (27.3)	11 (20.0)	35 (26.3)	23 (17.3)
White blood cell count decreased	14 (25.5)	7 (12.7)	13 (9.8)	8 (6.0)
Respiratory, thoracic and mediastinal disorders				
Cough	12 (21.8)	0	20 (15.0)	0
Dyspnoea	11 (20.0)	1 (1.8)	7 (5.3)	1 (0.8)
Skin and subcutaneous tissue disorders				
Alopecia	15 (27.3)	0	14 (10.5)	0

* Patients with PTCL treated with valemetostat 200 mg in the dose escalation part and dose expansion part

Serious adverse events reported in ≥2 patients in Study J101 (patients with PTCL treated with valemetostat 200 mg) were COVID-19, *Pneumocystis jirovecii* pneumonia, tumour associated fever, febrile neutropenia, hypercalcaemia, atrial fibrillation, pleural effusion, acute kidney injury, and pyrexia in 2 patients (3.6%) each. A causal relationship to valemetostat could not be ruled out for *Pneumocystis jirovecii* pneumonia in 2 patients and febrile neutropenia and acute kidney injury in 1 patient each. Adverse events leading to the interruption of valemetostat with an incidence of ≥5% were platelet count decreased, neutrophil count decreased, and COVID-19 in 4 patients (7.3%) each and dysgeusia in 3 patients (5.5%). There were no adverse events resulting in death. There were neither adverse events leading to treatment discontinuation nor dose reduction of valemetostat with an incidence of ≥5%.

Adverse events resulting in death in Study U202 (PTCL cohort) were disease progression in 7 patients (5.3%), general physical health deterioration, multiple organ dysfunction syndrome, pneumonia fungal, pneumonia bacterial, pseudomonal sepsis, intestinal perforation, hepatic failure, and haemophagocytic lymphohistiocytosis in 1 patient (0.8%) each, and a causal relationship to valemetostat was ruled out for all the events. Serious adverse events reported in ≥2 patients were disease progression in 7 patients (5.3%), COVID-19 pneumonia and general physical health deterioration in 3 patients (2.3%) each, and acute myeloid leukaemia, anaemia, COVID-19, diarrhoea, dyspnoea, haemophagocytic lymphohistiocytosis, platelet count decreased, pneumonia bacterial, and urinary tract infection in 2 patients (1.5%) each. A causal relationship to valemetostat could not be ruled out for diarrhoea in 2 patients, and anaemia, acute myeloid leukaemia, dyspnoea, haemophagocytic lymphohistiocytosis, and urinary tract infection in 1 patient (0.8%) each. Adverse events leading to the interruption of valemetostat with an incidence of ≥5% were platelet count decreased in 22 patients (16.5%), anaemia in 13 patients (9.8%), COVID-19 in 11 patients (8.3%), and neutrophil count decreased in 7 patients (5.3%). Adverse events leading to dose reduction of valemetostat with an incidence of ≥5% were platelet

count decreased in 7 patients (5.3%). There were no adverse events leading to treatment discontinuation of valemetostat with an incidence of ≥5%.

The applicant's explanation about difference in safety of valemetostat between Japanese and non-Japanese patients:
In Study U202 (PTCL cohort), all-grade adverse events with a ≥20% higher incidence in the Japanese patients than in the non-Japanese patients were platelet count decreased (12 Japanese patients [75.0%], 54 non-Japanese patients [46.2%]) and white blood cell count decreased (5 patients [31.3%], 8 patients [6.8%]). Grade ≥3 adverse events with a ≥10% higher incidence in the Japanese patients than in the non-Japanese patients were white blood cell count decreased (5 patients [31.3%], 3 patients [2.6%]) and neutrophil count decreased (5 patients [31.3%], 18 patients [15.4%]). An adverse event leading to the interruption of valemetostat with a ≥10% higher incidence in the Japanese patients than in the non-Japanese patients was pyrexia (2 patients [12.5%], 1 patient [0.9%]). There were no adverse events resulting in death, serious adverse events, or adverse events leading to the discontinuation or dose reduction of valemetostat with a ≥10% higher incidence in the Japanese patients than in the non-Japanese patients.

PMDA asked the applicant to explain differences in safety profile of valemetostat between patients with relapsed or refractory PTCL and patients with relapsed or refractory ATL, the approved indication.

The applicant's response:
Table 8 outlines safety of Study U202 in patients with relapsed or refractory PTCL (PTCL cohort) and Study J201 in patients with relapsed or refractory ATL.

Table 8. Outline of safety (Studies J201 and U202)

	Number of patients (%)	
	Study J201 (patients with ATL)	Study U202 (PTCL cohort)
	n = 25	n = 133
All adverse events	25 (100)	128 (96.2)
Grade ≥3 adverse events	15 (60.0)	77 (57.9)
Adverse events resulting in death	0	15 (11.3)
Serious adverse events	8 (32.0)	53 (39.8)
Adverse events leading to discontinuation of valemetostat	2 (8.0)	13 (9.8)
Adverse events leading to interruption	5 (20.0)	66 (49.6)
Adverse events leading to dose reduction	2 (8.0)	21 (15.8)

All-grade adverse events reported with a ≥20% higher incidence in Study U202 than in Study J201 were diarrhoea (39 patients [29.3%] in Study U202, 2 patients (8.0%) in Study J201) and COVID-19 (28 patients [21.1%], 0 patients). There were no Grade ≥3 adverse events, adverse events resulting in death, serious adverse events, or adverse events leading to the discontinuation, interruption, or dose reduction of valemetostat with a ≥10% higher incidence in Study U202 than in Study J201.

PMDA's review:
The serious adverse events and Grade ≥3 adverse events in patients with PTCL in Studies J101 and U202 require special attention during the use of valemetostat.

Although the limited number of Japanese patients precluded a definite conclusion on the difference in the safety of valemetostat between Japanese and non-Japanese patients based on the results of in Study U202, adverse events occurring at a higher incidence in Japanese patients than in non-Japanese patients are of attention. Furthermore, as compared with safety in patients with relapsed or refractory ATL, the approved indication, the adverse events occurring at a higher incidence in patients with PTCL also warrant attention.

However, they are generally known adverse events of valemetostat, and valemetostat will be tolerable in patients with relapsed or refractory PTCL when appropriate measures, such as adverse event monitoring and management, the interruption, dose reduction, and discontinuation of valemetostat, are taken by physicians with adequate knowledge and experience in treatment of hematopoietic malignancy.

7.R.4 Clinical positioning and indications

The proposed indication of valemetostat was "relapsed or refractory peripheral T-cell lymphoma." The "Precautions Concerning Indications" section include the following advice:

- Definitive diagnosis of the disease to be treated with valemetostat should be made by physicians or at facilities adequately experienced in pathological diagnosis.
- Physicians should be well-versed in the information provided in the "Clinical Studies" section, including the histopathological types of the patients enrolled in the clinical studies, and have a full understanding of the efficacy and safety of valemetostat so as to select eligible patients.

As a result of the discussion in Sections "7.R.2 Efficacy," "7.R.3 Safety," and the following section, PMDA has concluded that the proposed Indications and Precautions Concerning Indications sections for valemetostat are appropriate.

7.R.4.1 Clinical positioning of valemetostat

Japanese and foreign clinical practice guidelines[15)] or major textbooks[16)] on hematology contain no descriptions about the use of valemetostat in patients with relapsed or refractory PTCL.

The applicant's explanation about clinical positioning of valemetostat in treatment of relapsed or refractory PTCL:

Relapsed or refractory PTCL is an extremely rare disease with poor prognosis. In Japan, there are no confirmatory study results of the approved antineoplastic agents[17)] for relapsed or refractory PTCL, or no standard therapy has been established. In such situation, Study U202 conducted as an uncontrolled study demonstrated the clinical usefulness of valemetostat [see Sections 7.R.2 and 7.R.3], and valemetostat is considered as one of the treatment options for this patient population.

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15) National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, T-Cell Lymphomas (NCCN Guidelines) (v.1.2023) and Practical Guidelines for Hematological Malignancies 2023, by the Japanese Society of Hematology

16) Wintrobe's Clinical Hematology 14th Edition (Lippincott Williams & Wilkins, 2018, USA) and Williams Hematology 10th Edition (McGraw Hill Medical, 2021, USA)

17) Mogamulizumab (genetical recombination), forodesine hydrochloride, pralatrexate, romidepsin, brentuximab vedotin (genetical recombination), denileukin diftitox (genetical recombination), tucidinostat, and darinaparsin

The choice between valemetostat and the other antineoplastic agents[17] is expected to be made appropriately by healthcare professionals based on the mechanism of action, efficacy, and safety of each drug as well as the condition of each patient, in view of no available clinical study data comparing clinical usefulness of valemetostat with these agents.

PMDA accepted the applicant's explanation.

7.R.4.2 Patient eligibility and indication of valemetostat

The applicant's explanation about histopathological types of patients eligible for valemetostat:
In Study J101, various types of PTCL responded to valemetostat. Therefore, the inclusion criteria of Study U202 specified the types of PTCL.[18] The disease types that require different treatment systems[19] were specified in the exclusion criteria.

Table 9 shows the response rate based on central assessment according to the criteria for response assessment in the Lugano classification by histopathological type included in Study U202. Among the types of PTCL, angioimmunoblastic T-cell lymphoma (AITL), PTCL not otherwise specified (PTCL-NOS), anaplastic lymphoma kinase (ALK)-negative anaplastic large cell lymphoma (ALCL), nodal PTCL with T follicular helper cells (PTCL-TFH), and follicular T-cell lymphoma (FTCL) responded to valemetostat. Thus, valemetostat has promising efficacy against these histopathological types.

Table 9. Best overall response and response rate by histopathological type (PTCL cohort in Study U202, central assessment, efficacy analysis population)

Histopathological type[*1]	Number of patients (%)	Best overall response				Response (CR or PR) (response rate [%])
		CR	PR	SD	PD	
AITL	42 (35.3)	8	15	10	5	23 (54.8)
PTCL-NOS	41 (34.5)	4	9	8	10	13 (31.7)
ALK-negative ALCL	7 (5.9)	1	2	1	2	3 (42.9)
PTCL-TFH	8 (6.7)	1	3	1	2	4 (50.0)
FTCL	3 (2.5)	2	0	0	1	2 (66.7)
ALK-positive ALCL	2 (1.7)	0	0	0	1	0
MEITL	1 (0.8)	0	0	0	1	0
CD8-positive AECTCL	1 (0.8)	0	0	0	1	0
PCGDTCL	1 (0.8)	0	0	0	1	0
Others[*2]	13 (10.9)	1	6	1	3	7 (53.8)

*1 The disease types that were eligible for Study U202 but resulting in no patient enrolled were enteropathy-associated T-cell lymphoma (EATL) and hepatosplenic T-cell lymphoma (HSTL).
*2 T-cell lymphoma with an undetermined histopathological type despite its eligibility for inclusion confirmed by central assessment

The following observations support the possible inclusion of the histopathological types that were excluded or did not respond to valemetostat in Study U202 as eligible types for valemetostat:

- The progression of PTCL is associated with down-regulation of tumor suppressor gene expression induced by excessive trimethylation of the lysine residue at position 27 of histone H3 (histone H3 lysine 27 [H3K27]) (*Cell Rep.* 2019;29:2321-37). Valemetostat inhibits the excessive trimethylation

18) The inclusion criteria specified the eligible types of PTCL as follows: Enteropathy-associated T-cell lymphoma (EATL), monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL), hepatosplenic T-cell lymphoma (HSTL), primary cutaneous gamma delta T cell lymphoma (PCGDTCL), primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma (CD8-positive AECTCL), PTCL-NOS, AITL, FTCL, PTCL-TFH, ALK-positive ALCL, and ALK-negative ALCL.

19) Mycosis fungoides, Sezary syndrome, primary cutaneous ALCL, precursor T-cell leukemia and lymphoma, T-cell prolymphocytic leukemia, and T-cell large granular lymphocytic leukemia

of H3K27 by simultaneously inhibiting EZH1 and EZH2 and is thereby expected to inhibit tumor growth of PTCL irrespective of histopathological type.

- Of the histopathological types excluded from Study U202, extranodal NK/T-cell lymphoma, nasal type (ENKL) and subcutaneous panniculitis-like T-cell lymphoma (SPTCL) were evaluated in Study J101. The study enrolled 1 patient with ENKL and 2 patients with SPTCL, of whom 1 patient each responded to valemetostat (partial response [PR]).
- ALK-positive ALCL, monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL)], primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma (CD8-positive AECTCL), and primary cutaneous gamma delta T cell lymphoma (PCGDTCL) were included in Study U202 but poorly responded to valemetostat. The limited number of patients with these histopathological types in the study precluded a definite conclusion on the efficacy of valemetostat against these types. However, in view of a certain degree of efficacy observed against some of these histopathological types, valemetostat has promising efficacy in patients with these histopathological types.

Based on the above, the indication of valemetostat may be defined as "relapsed or refractory peripheral T-cell lymphoma" when the package insert elaborates the histopathological types actually included in Study U202 and provides the efficacy data by histopathological type in the "Clinical Studies" section, along with the following cautionary advice in the "Precautions Concerning Indications" section. In addition, definitive diagnosis of the disease to be treated with valemetostat must be made by physicians or at facilities with adequate experience in pathological diagnosis, and the package insert will also offer advice to this effect.

- Physicians should be well-versed in the information presented in the "Clinical Studies" section, including the histopathological types of the patients enrolled in the clinical studies, and have a full understanding of the efficacy and safety of valemetostat so as to select eligible patients.

PMDA's review:

Based on the applicant's explanation about the histopathological types to be treated with valemetostat and the following observations, the proposed indication of valemetostat described as "relapsed or refractory peripheral T-cell lymphoma" is acceptable when the package insert provides details of patient population in Study U202 in the "Clinical Studies" section and cautionary advice in the "Precautions Concerning Indications" as mentioned earlier by the applicant.

- There is no established standard therapy that potentially extends OS of patients with relapsed or refractory PTCL [see Section 7.R.4.1] or that is tailored to each histopathological type.
- The extremely limited number of patients with relapsed or refractory PTCL precludes conducting a clinical study by histopathological type to evaluate the efficacy, etc. of valemetostat.
- Valemetostat is a drug to be prescribed by physicians with adequate knowledge and experience in treatment of hematopoietic malignancy, and eligibility for valemetostat should be appropriately determined based on the condition of each patient.

7.R.5 Dosage and administration

The proposed dosage and administration of valemetostat was "the usual adult dosage is 200 mg of valemetostat orally administered once daily in the fasted state. The dose may be reduced according to

the patient's condition," as previously defined for the approved indication. In addition, the "Precautions Concerning Dosage and Administration" section includes the following statements.

Precautions Concerning Dosage and Administration

- The efficacy and safety of valemetostat used in combination with other antineoplastic agents have not been established.
- Decreased C_{max} and AUC were reported with valemetostat administered after meal. In order to avoid food effect, the use of valemetostat should be avoided from 1 hour before until 2 hours after meal.
- Criteria for dose adjustment in response to adverse drug reactions
- Dose of valemetostat in concomitant use with potent CYP3A inhibitor or P-gp inhibitor

As a result of the discussion in Sections "7.R.2 Efficacy," "7.R.3 Safety," and the following subsection, PMDA has concluded that the "Dosage and Administration" and "Precautions Concerning Dosage and Administration" sections for relapsed or refractory PTCL should be described as below, as per the proposal.[20)]

Dosage and Administration

The usual adult dosage is 200 mg of valemetostat orally administered once daily in the fasted state. The dose may be reduced according to the patient's condition.

Precautions Concerning Dosage and Administration

- The efficacy and safety of valemetostat used in combination with other antineoplastic agents have not been established.
- Decreased C_{max} and AUC were reported with valemetostat administered after meal. In order to avoid food effect, the use of valemetostat should be avoided from 1 hour before until 2 hours after meal.
- When any adverse drug reaction of valemetostat occurs, valemetostat should be interrupted, reduced in dose, or discontinued according to the following criteria. The dose should not be reduced by >2 dose levels in response to an adverse drug reaction.

Dose of valemetostat for dose reduction or discontinuation

Dose level	Dose
Dose level 1	200 mg
Dose level 2	150 mg
Dose level 3	100 mg
Dose level 4	50 mg
Discontinuation	If valemetostat 50 mg is intolerable, discontinue the treatment.

[20] The same setting as that for the approved indication, except for the criteria for dose adjustment in response to adverse drug reactions

Criteria for dose adjustment of valemetostat (relapsed or refractory PTCL)

Adverse drug reaction	Severity	Measure
Neutrophil count decreased	Neutrophil count <500/mm^3	Interrupt valemetostat until the neutrophil count recovers to ≥1,000/mm^3. After recovery from the symptom persisting for ≤7 days, resume valemetostat where necessary at the dose interrupted, or at the dose 1-dose-level lower than the dose interrupted after recovery from the symptom persisting for >7 days. After necessary interruption and recovery thereafter, resume valemetostat where necessary at the dose 1-dose-level lower than the previous dose.
Platelet count decreased	Platelet count <50,000/mm^3 persisting for >7 days	Interrupt valemetostat until the platelet count recovers to ≥50,000/mm^3. After recovery, resume valemetostat where necessary at the dose interrupted. If the symptom recurs after resumption, interrupt valemetostat until the platelet count recovers to ≥50,000/mm^3. After recovery, resume valemetostat where necessary at the dose 1-dose-level lower than the previous dose. If the symptom recurs after resumption at the reduced dose, discontinue valemetostat.
	Platelet count <50,000/mm^3 accompanied by Grade ≥2* haemorrhage	Interrupt valemetostat until the platelet count recovers to ≥50,000/mm^3. After recovery, resume valemetostat where necessary at the dose 1-dose-level lower than the dose interrupted. If the symptom recurs after resumption, discontinue valemetostat.
	Platelet count <25,000/mm^3	Interrupt valemetostat until the platelet count recovers to ≥50,000/mm^3. After recovery, resume valemetostat where necessary at the dose 1-dose-level lower than the dose interrupted. After necessary interruption and recovery thereafter, resume valemetostat where necessary at the dose 1-dose-level lower than the previous dose.
Anaemia	Hemoglobin value <8.0 g/dL, requiring red blood cell transfusion	Interrupt valemetostat until the hemoglobin value recovers to ≥8.0 g/dL after ≥7 days from the last transfusion. After recovery, resume valemetostat where necessary at the dose interrupted. After necessary interruption and recovery thereafter, resume valemetostat where necessary at the dose 1-dose-level than the previous dose.
Non-hematotoxicity	Grade 3,* requiring treatment	Interrupt valemetostat until recovery to Grade ≤1*or baseline. After recovery, resume valemetostat where necessary at the dose interrupted. When the same adverse drug reaction leads to subsequent interruption, resume valemetostat where necessary after recovery at the dose 1-dose-level lower than the previous dose.
	Grade 4*	Interrupt valemetostat until recovery to Grade ≤1*or baseline. After recovery, resume valemetostat where necessary at the dose 1-dose-level lower than the dose interrupted. When the same adverse drug reaction leads to subsequent interruption, discontinue valemetostat.

* Graded as per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE).

- Concomitant use of a potent CYP3A inhibitor or P-gp inhibitor may increase blood valemetostat concentration. The use of valemetostat should be considered with reference to the following criteria.

Criteria for dose adjustment of valemetostat when administered concomitantly with CYP3A inhibitor or P-gp inhibitor

Concomitant drug	Dose of valemetostat		
	200 mg	150 or 100 mg	50 mg
Potent CYP3A inhibitor	Reduce to 100 mg	Reduce to 50 mg	Do not use valemetostat concomitantly.
P-gp inhibitor			
Drug that potently inhibits CYP3A and P-gp	Reduce to 50 mg	Do not use valemetostat concomitantly.	

7.R.5.1 Dosage and administration of valemetostat and dose adjustment

The applicant's explanation about the dosage regimen of valemetostat and dose adjustment:

The dosage regimen of valemetostat in Study U202 was specified as 200 mg orally administered in the fasted state QD, as a result of dose exploration in Study J101 that had indicated valemetostat 200 mg QD as recommended dose for patients with relapsed or refractory PTCL [see Section 7.1.1.1].

Study U202 with the above dosage regimen demonstrated the clinical usefulness of valemetostat in patients with relapsed or refractory PTCL. The proposed dosage and administration of valemetostat were determined based on this regimen.

In Study U202, valemetostat was used in accordance with the pre-determined criteria for interruption, dose reduction, or discontinuation of valemetostat in response to adverse drug reactions and was tolerable. The "Precautions Concerning Dosage and Administration" section provides the dose adjustment criteria of valemetostat based on those in this study. In Study U202, the dose adjustment criteria of valemetostat in response to QT interval prolonged[21)] and febrile neutropenia[22)] were provided, but these events occurred in extremely limited number of patients, and a relationship of these events to valemetostat remains unclear at present. Therefore, the dose adjustment criteria in response to QT interval prolonged and febrile neutropenia in Study U202 are not specifically provided.

PMDA accepted the applicant's explanation.

7.R.6 Post-marketing investigations

The applicant's explanation about post-marketing surveillance plan:
In order to investigate the safety of valemetostat in post-marketing clinical use, the applicant plans to conduct all-case post-marketing surveillance in patients with relapsed or refractory PTCL treated with valemetostat.

The safety specifications of the surveillance are myelosuppression, infections, and secondary malignant tumor, which are events of special attention in the treatment with valemetostat, in view of incidences of adverse events in Studies J101 and U202.

The planned sample size is 150 patients, in view of the incidences of the above safety specification events in Studies J101 and U202.

The observation period is 1 year for myelosuppression and infections and 3 years for secondary malignant tumor, in view of time to onset of these events in Studies J101 and U202.

PMDA's review:
In light of the following observations, the post-marketing surveillance should be conducted in all patients treated with valemetostat for a certain time period after its launch to collect the safety data promptly in an unbiased manner, and healthcare professionals should be immediately updated with new safety information.

- Extremely limited safety data are available from Japanese patients with relapsed or refractory PTCL treated with valemetostat in the clinical studies.

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21) If Grade 3 QT interval prolonged occurs, interrupt valemetostat until the symptom recovers to Grade ≤1; and if the event is causally related to valemetostat, resume valemetostat at one-level lower dose than the previous dose.
22) If Grade ≥3 febrile neutropenia occurs, interrupt valemetostat; and after the neutrophil count recovers to $\geq 1.0 \times 10^9$/L, resume valemetostat (at a reduced dose where necessary).

- Despite the ongoing all-case surveillance planned at the initial approval, extremely limited post-marketing safety data of valemetostat have been obtained from patients in Japan.[23)]

The safety specifications, planned sample size, and observation period of the surveillance planned by the applicant are acceptable.

7.2 Adverse events, etc. observed in clinical studies

The clinical study data on deaths submitted for the safety evaluation were detailed in Section "7.1 Evaluation data." The following subsection summarizes major adverse events other than deaths.

7.2.1 Global phase I study (Study J101)

7.2.1.1 Dose escalation part

Adverse events and adverse events for which a causal relationship to valemetostat could not be ruled out were reported in all patients. Adverse events with an incidence of ≥30% were platelet count decreased in 21 patients (84.0%), dysgeusia in 16 patients (64.0%), lymphocyte count decreased in 15 patients (60.0%), anaemia in 13 patients (52.0%), neutrophil count decreased and white blood cell count decreased in 11 patients (44.0%) each, alopecia in 10 patients (40.0%), alanine aminotransferase (ALT) increased in 9 patients (36.0%), nasopharyngitis, diarrhoea, and rash in 8 patients (32.0%) each.

Serious adverse events occurred in 6 of 25 patients (24.0%). Serious adverse events reported in ≥2 patients were *Pneumocystis jirovecii* pneumonia and liver disorder in 2 patients (8.0%) each. A causal relationship to valemetostat could not be ruled out for *Pneumocystis jirovecii* pneumonia in 2 patients.

An adverse event leading to discontinuation of valemetostat occurred in 1 of 25 patients (4.0%). There were no adverse events leading to discontinuation of valemetostat reported in ≥2 patients.

7.2.1.2 Dose expansion part

Adverse events occurred in all patients. Adverse events for which a causal relationship to valemetostat could not be ruled out occurred in 43 of 53 patients (81.1%) in the PTCL cohort and 10 of 12 patients (83.3%) in the ATL cohort. Adverse events with an incidence of ≥30% were platelet count decreased in 29 patients (54.7%), dysgeusia in 23 patients (43.4%), and anaemia in 22 patients (41.5%) in the PTCL cohort; and platelet count decreased in 8 patients (66.7%), dysgeusia and neutrophil count decreased in 6 patients (50.0%) each, alopecia in 5 patients (41.7%), and dry skin, pruritus, arthralgia, and anaemia in 4 patients (33.3%) each in the ATL cohort.

Serious adverse events occurred in 26 of 53 patients (49.1%) in the PTCL cohort and 7 of 12 patients (58.3%) in the ATL cohort. Serious adverse events reported in ≥2 patients were COVID-19, *Pneumocystis jirovecii* pneumonia, febrile neutropenia, hypercalcaemia, atrial fibrillation, pleural effusion, and acute kidney injury in 2 patients (3.8%) each in the PTCL cohort (no applicable events in the ATL cohort). A causal relationship to valemetostat could not be ruled out for *Pneumocystis jirovecii* pneumonia in 2 patients and febrile neutropenia in 1 patient.

[23)] The post-marketing surveillance is ongoing involving all patients treated with valemetostat, and the number of patients with the survey form data fixed is 0 (of 100 patients enrolled) (as of September 25, 2023).

Adverse events leading to discontinuation of valemetostat occurred in 6 of 53 patients (11.3%) in the PTCL cohort (no applicable events in the ATL cohort). There were no adverse events leading to discontinuation of valemetostat reported in ≥2 patients.

7.2.1.3 DDI cohort

Adverse events occurred in all patients. Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 21 of 24 patients (87.5%). Adverse events with an incidence of ≥30% were dysgeusia in 12 patients (50.0%), diarrhoea, anaemia, and platelet count decreased in 11 patients (45.8%), and neutrophil count decreased in 8 patients (33.3%).

Serious adverse events occurred in 7 of 24 patients (29.2%). Serious adverse events reported in ≥2 patients were disease progression in 2 patients (8.3%), and its causal relationship to the study drug was ruled out.

There were no adverse events leading to discontinuation of the study drug.

7.2.2 Global phase II study (Study U202)

7.2.2.1 PTCL cohort

Adverse events occurred in 128 of 133 patients (96.2%). Adverse events for which a causal relationship to valemetostat could not be ruled out occurred in 106 of 133 patients (79.7%). Adverse events with an incidence of ≥20% were platelet count decreased in 66 patients (49.6%), anaemia in 47 patients (35.3%), diarrhoea in 39 patients (29.3%), dysgeusia in 38 patients (28.6%), neutrophil count decreased in 35 patients (26.3%), and COVID-19 in 28 patients (21.1%).

Serious adverse events occurred in 53 of 133 patients (39.8%). Serious adverse events reported in ≥2 patients were disease progression in 7 patients (5.3%), COVID-19 pneumonia and general physical health deterioration in 3 patients (2.3%) each, and acute myeloid leukaemia, anaemia, COVID-19, diarrhoea, dyspnoea, haemophagocytic lymphohistiocytosis, platelet count decreased, pneumonia bacterial, and urinary tract infection in 2 patients (1.5%) each. A causal relationship to valemetostat could not be ruled out for diarrhoea in 2 patients, and anaemia, acute myeloid leukaemia, dyspnoea, haemophagocytic lymphohistiocytosis, and urinary tract infection in 1 patient each.

Adverse events leading to discontinuation of valemetostat occurred in 13 of 133 patients (9.8%). Adverse events leading to discontinuation of valemetostat reported in ≥2 patients were platelet count decreased in 3 patients (2.3%) and acute myeloid leukaemia in 2 patients (1.5%). A causal relationship to valemetostat could not be ruled out for platelet count decreased in 3 patients and acute myeloid leukaemia in 1 patient.

7.2.2.2 ATL cohort

Adverse events occurred in all patients. Adverse events for which a causal relationship to valemetostat could not be ruled out occurred in 17 of 22 patients (77.3%). Adverse events with an incidence of ≥20% were platelet count decreased in 13 patients (59.1%), anaemia in 11 patients (50.0%), hypercalcaemia,

diarrhoea, and neutrophil count decreased in 6 patients (27.3%) each, and COVID-19 and dysgeusia in 5 patients (22.7%) each.

Serious adverse events occurred in 15 of 22 patients (68.2%). Serious adverse events reported in ≥2 patients were disease progression in 3 patients (13.6%) and COVID-19 and diarrhoea in 2 patients (9.1%) each. A causal relationship to valemetostat could not be ruled out for COVID-19 in 1 patient.

Adverse events leading to discontinuation of valemetostat occurred in 2 of 22 patients (9.1%). There were no adverse events leading to discontinuation of valemetostat reported in ≥2 patients.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.2-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that valemetostat has efficacy in the treatment of relapsed or refractory PTCL, and that valemetostat has acceptable safety in view of its benefits. Valemetostat is of clinical significance as a treatment option for relapsed or refractory PTCL. The clinical positioning of valemetostat is subject to further review.

PMDA has concluded that valemetostat may be approved if valemetostat is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

April 24, 2024

Product Submitted for Approval

Brand Name	Ezharmia Tablets 50 mg Ezharmia Tablets 100 mg
Non-proprietary Name	Valemetostat Tosilate
Applicant	Daiichi Sankyo Company, Limited
Date of Application	January 31, 2024

List of Abbreviations
See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Efficacy

As a result of the discussion in Section "7.R.2 Efficacy" of the Review Report (1), PMDA concluded that the efficacy of valemetostat had been demonstrated to a certain degree in patients with relapsed or refractory PTCL in the global phase II study (Study U202) targeting this patient population. The result of the primary endpoint, namely, the centrally-assessed response rate [95% CI] according to the criteria for response assessment in the Lugano classification, was 43.7 [34.6, 53.1] (52 of 119 patients), and the lower limit of the 95% CI exceeded the pre-determined threshold response rate (27%).

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

1.2 Safety

As a result of the discussion in Section "7.R.3 Safety" of the Review Report (1), PMDA concluded that adverse events requiring special attention during the treatment with valemetostat are those (myelosuppression, infections, and secondary malignant tumor) which were identified as such in the previous review for the approved indication.

PMDA concluded that valemetostat is tolerable, albeit the above-mentioned adverse events warranting attention during the treatment, when appropriate measures, i.e., adverse event monitoring and

management, the interruption, dose reduction, and discontinuation of valemetostat, are taken by physicians with adequate knowledge and experience in treatment of hematopoietic malignancy.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

1.3 Clinical positioning and indications

As a result of the discussion in Section "7.R.4 Clinical positioning and indications" of the Review Report (1), PMDA concluded that the indication of valemetostat should be defined as "relapsed or refractory peripheral T-cell lymphoma" as proposed, and the "Clinical Studies" section in the package insert should include the information on the histopathological types enrolled in Study U202, the histopathological types actually evaluated, and the results on the efficacy by histopathological type; along with the following advice in the "Precautions Concerning Indications" section.

Precautions Concerning Indications

- Definitive diagnosis of the disease to be treated with valemetostat should be made by physicians or at facilities adequately experienced in pathological diagnosis.
- Physicians should be well-versed in the information provided in the "Clinical Studies" section, including the histopathological types of the patients enrolled in the clinical studies, and have a full understanding of the efficacy and safety of valemetostat so as to select eligible patients.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

1.4 Dosage and administration

As a result of the discussion in Section "7.R.5 Dosage and administration" of the Review Report (1), PMDA concluded that the Dosage and Administration and Precautions Concerning Dosage and Administration sections should be described as below as per the proposal.

Dosage and Administration

The usual adult dosage is 200 mg of valemetostat orally administered once daily in the fasted state. The dose may be reduced according to the patient's condition.

Precautions Concerning Dosage and Administration

- The efficacy and safety of valemetostat used in combination with other antineoplastic agents have not been established.
- Decreased C_{max} and AUC were reported with valemetostat administered after meal. In order to avoid food effect, the use of valemetostat should be avoided from 1 hour before until 2 hours after meal.
- Criteria for dose adjustment in response to adverse drug reactions
- Dose of valemetostat in concomitant use with potent CYP3A inhibitor or P-gp inhibitor

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

1.5 Risk management plan (draft)

In order to investigate the safety of valemetostat in post-marketing clinical use, the applicant plans to conduct a post-marketing surveillance in all patients with relapsed or refractory PTCL treated with valemetostat. The planned sample size is 150 patients. The observation period is 1 year for myelosuppression and infections and 3 years for secondary malignant tumor, both after the first dose of valemetostat.

As a result of the discussion in Section "7.R.6 Post-marketing investigations" of the Review Report (1), PMDA concluded that the post-marketing surveillance should be conducted covering all patients with relapsed or refractory PTCL treated with valemetostat for a certain time period after its launch to collect the safety information in prompt and unbiased manner, and healthcare professionals should be immediately updated with new safety information.

PMDA further concluded that the safety specifications, planned sample size, and observation period of the surveillance planned by the applicant are acceptable.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

In view of the discussion above, PMDA has concluded that the risk management plan (draft) for valemetostat should include the safety specifications presented in Table 10, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities according to Tables 11 and 12.

Table 10. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Myelosuppression • Infections • Drug interactions with CYP3A inhibitors and P-gp inhibitors	• Secondary malignant tumor • Reproductive and developmental toxicity	Not applicable
Efficacy specification		
Not applicable		

No changes for the present partial change application

Table 11. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Efficacy survey and studies	Additional risk minimization activities
• Use-results survey in patients with relapsed or refractory ATL (all-case surveillance) • <u>Use-results survey in patients with relapsed or refractory PTCL (all-case surveillance)</u>	Not applicable	• <u>Preparation and distribution of materials for healthcare professionals</u>

Underline denotes activities to be conducted for the additional indication.

Table 12. Outline of use-results survey (draft)

Objective	To investigate safety of valemetostat in post-marketing settings
Survey method	All-case surveillance
Population	All patients with relapsed or refractory PTCL treated with valemetostat
Observation period	1 year for myelosuppression and infections 3 years for secondary malignant tumor
Planned sample size	150
Main survey items	Safety specification: Myelosuppression, infections, and secondary malignant tumor Other main survey items: Patient characteristics (age, sex, histopathological type, medical history, complications, etc.), prior treatment, use status of valemetostat, concomitant drugs, adverse events, etc.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indications and dosage and administration defined below, with the following approval conditions, when it is assured that the package insert offers appropriate cautionary advice, information about proper use is disseminated appropriately in the post-marketing setting, and valemetostat is properly used by physicians with adequate knowledge and experience in treatment of hematopoietic malignancy and at medical institutions capable of emergency response. The product was designated as a SAKIGAKE designation drug with the intended indication of "relapsed or refractory peripheral T-cell lymphoma" ("The Fourth Trial Implementation of the SAKIGAKE Designation System for Drugs (in Japanese)," PSEHB/PED Notification No. 0907-1 dated September 7, 2018). However, the remainder of the previously-granted re-examination period exceeds 6 years, and for this reason, etc., the re-examination period for the present application should be the remainder of the re-examination period for the product's initial approval (until September 25, 2032).

Indications (Underline denotes additions.)
Relapsed or refractory adult T-cell leukemia-lymphoma
<u>Relapsed or refractory peripheral T-cell lymphoma</u>

Dosage and Administration (No change)
The usual adult dosage is 200 mg of valemetostat orally administered once daily in the fasted state. The dose may be reduced according to the patient's condition.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Given the extremely limited number of Japanese patients participated in clinical studies, the applicant is required to conduct a drug use-results survey involving all Japanese patients treated with the product after the market launch until data are gathered from a certain number of patients to understand the characteristics of patients using the product, and to promptly collect safety and efficacy data so that necessary measures are taken to ensure proper use of the product.

Warnings
The product should be administered at medical institutions capable of emergency response, only when patients are found to be eligible for the treatment with the product by a physician with sufficient knowledge and experience in treatment of hematopoietic malignancy. Prior to treatment, the benefits

and risks of the treatment should be thoroughly explained to the patient or their family, and consent should be obtained.

Contraindication

Patients with a history of hypersensitivity to any ingredient of the product

Precautions Concerning Indications (Underline denotes additions.)

Relapsed or refractory adult T-cell leukemia-lymphoma

1. Physicians should be well-versed in the information in the "Clinical Studies" section, including the disease types of the patients enrolled in the clinical studies and the presence or absence of poor prognostic factors in these patients, and have full understanding of the efficacy and safety of valemetostat so as to select eligible patients.

Relapsed or refractory peripheral T-cell lymphoma

2. Definitive diagnosis of the disease to be treated with valemetostat should be made by physicians or at facilities with adequate experience in pathological diagnosis.
3. Physicians should be well-versed in the information in the "Clinical Studies" section, including the histopathological types of the patients enrolled in the clinical studies, and have full understanding of the efficacy and safety of valemetostat so as to select eligible patients.

Precautions Concerning Dosage and Administration (Underline denotes additions, and strikethrough denotes deletions.)

1. The efficacy and safety of valemetostat used in combination with other antineoplastic agents have not been established.
2. Decreased C_{max} and AUC were reported with valemetostat administered after meal. In order to avoid food effect, the use of valemetostat should be avoided from 1 hour before until 2 hours after meal.
3. When any adverse reaction of valemetostat occurs, valemetostat should be interrupted, reduced in dose, or discontinued according to the following criteria. The dose should not be reduced by >2 dose levels in response to ~~the same~~ adverse drug reactions.

Relapsed or refractory adult T-cell leukemia-lymphoma/peripheral T-cell lymphoma

- Dose reduction or discontinuation

~~Dose reduction levels of valemetostat~~

~~Level~~ Dose level	Dose
~~Usual dose~~ Dose level 1	200 mg
~~1-level reduced dose~~ Dose level 2	150 mg
~~2-level reduced dose~~ Dose level 3	100 mg
~~3-level reduced dose~~ Dose level 4	50 mg
~~4-level reduced dose~~ Discontinuation	~~Discontinuation~~ If valemetostat 50 mg is intolerable, discontinue the treatment.

Relapsed or refractory adult T-cell leukemia-lymphoma

- Dose adjustment criteria of valemetostat in response to adverse drug reactions

~~Criteria for dose adjustment of valemetostat~~

Adverse drug reaction	Severity	Measure
Neutrophil count decreased	Neutrophil count <500/mm^3 persisting for >7 days	Interrupt valemetostat until the neutrophil count recovers to ≥1,000/mm^3 or baseline. After recovery, resume valemetostat where necessary at the dose interrupted. If the symptom recurs after resumption, interrupt valemetostat until the neutrophil count recovers to ≥1,000/mm^3 or baseline. After recovery, resume valemetostat where necessary at the dose 1-dose-level lower than the previous dose.
Platelet count decreased	Platelet count <25,000/mm^3	Interrupt valemetostat until the platelet count recovers to ≥50,000/mm^3 or baseline. After recovery, resume valemetostat where necessary at the dose interrupted. If the symptom recurs after resumption, interrupt valemetostat until the platelet count recovers to ≥50,000/mm^3 or baseline. After recovery, resume valemetostat where necessary at the dose 1-dose-level lower than the previous dose.
Anaemia	Hemoglobin value <8.0 g/dL, requiring red blood cell transfusion	Interrupt valemetostat until the hemoglobin value recovers to ≥8.0 g/dL or baseline. After recovery, resume valemetostat where necessary at the dose interrupted. If the symptom recurs after resumption, interrupt valemetostat until the hemoglobin value recovers to ≥8.0 g/dL or baseline. After recovery, resume valemetostat where necessary at the dose 1-dose-level lower than the previous dose.
Non-haematotoxicity	Grade ≥3[Note)]	Interrupt valemetostat until recovery to Grade ≤1[Note)] or baseline. After recovery, resume valemetostat where necessary at the dose interrupted. If the symptom recurs after resumption, interrupt valemetostat until recovery to Grade ≤1[Note)] or baseline. After recovery, resume valemetostat where necessary at the dose 1-dose-level lower than the previous dose.

Note) Graded as per the NCI-CTCAE.

Relapsed or refractory peripheral T-cell lymphoma

- Dose adjustment criteria of valemetostat in response to adverse drug reactions

Adverse drug reaction	Severity	Measure
Neutrophil count decreased	Neutrophil count <500/mm^3	Interrupt valemetostat until the neutrophil count recovers to ≥1,000/mm^3. After recovery from the symptom persisting for ≤7 days, resume valemetostat where necessary at the dose interrupted, or at the dose 1-dose-level lower than the dose interrupted after recovery from the symptom persisting for >7 days. After necessary interruption and recovery thereafter, resume valemetostat where necessary at the dose 1-dose-level lower than the previous dose.
Platelet count decreased	Platelet count <50,000/mm^3 persisting for >7 days	Interrupt valemetostat until the platelet count recovers to ≥50,000/mm^3. After recovery, resume valemetostat where necessary at the dose interrupted. If the symptom recurs after resumption, interrupt valemetostat until the platelet count recovers to ≥50,000/mm^3. After recovery, resume valemetostat where necessary at the dose 1-dose-level lower than the previous dose. If the symptom recurs after resumption at the reduced dose, discontinue valemetostat.
	Platelet count <50,000/mm^3 accompanied by Grade ≥2[Note)] haemorrhage	Interrupt valemetostat until the platelet count recovers to ≥50,000/mm^3. After recovery, resume valemetostat where necessary at the dose 1-dose-level lower than the dose interrupted. If the symptom recurs after resumption, discontinue valemetostat.
	Platelet count <25,000/mm^3	Interrupt valemetostat until the platelet count recovers to ≥50,000/mm^3. After recovery, resume valemetostat where necessary at the dose 1-dose-level lower than the dose interrupted. After necessary interruption and recovery thereafter, resume valemetostat where necessary at the dose 1-dose-level lower than the previous dose.
Anaemia	Hemoglobin value <8.0 g/dL, requiring red blood cell transfusion	Interrupt valemetostat until the hemoglobin value recovers to ≥8.0 g/dL after ≥7 days from the last transfusion. After recovery, resume valemetostat where necessary at the dose interrupted. After necessary interruption and recovery thereafter, resume valemetostat where necessary at the dose 1-dose-level lower than the previous dose.
Non-haematotoxicity	Grade 3,[Note)] requiring treatment	Interrupt valemetostat until recovery to Grade ≤1[Note)] or baseline. After recovery, resume valemetostat where necessary at the dose interrupted. Thereafter, when the same adverse drug reaction leads to subsequent interruption, resume valemetostat after recovery where necessary at the dose 1-dose-level lower than the previous dose.
	Grade 4[Note)]	Interrupt valemetostat until recovery to Grade ≤1[Note)] or baseline. After recovery, resume valemetostat where necessary at the dose 1-dose-level lower than the dose interrupted. When the same adverse drug reaction leads to subsequent interruption, discontinue valemetostat.

Note) Graded as per the NCI-CTCAE.

4. Concomitant use of a potent CYP3A inhibitor or P-glycoprotein (P-gp) inhibitor may increase blood concentrations of valemetostat. The use of valemetostat should be considered with reference to the following criteria.

Criteria for dose adjustment of valemetostat when administered concomitantly with CYP3A inhibitor or P-gp inhibitor

Concomitant drug	Dose of valemetostat		
	200 mg	150 or 100 mg	50 mg
Potent CYP3A inhibitor	Reduce to 100 mg	Reduce to 50 mg	Do not use valemetostat concomitantly.
P-gp inhibitor			
Drug that potently inhibits CYP3A and P-gp	Reduce to 50 mg	Do not use valemetostat concomitantly.	

Appendix

List of Abbreviations

AITL	angioimmunoblastic T-cell lymphoma
ALCL	anaplastic large cell lymphoma
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ATL	adult T-cell leukemia/lymphoma
ATP	adenosine triphosphate
CD8-positive AECTCL	primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma
CI	confidence interval
COVID-19	corona virus infectious disease emerged in 2019
CR	complete response
CT	computed tomography
CYP	cytochrome P450
DDI	drug-drug interaction
DLT	dose limiting toxicity
EATL	enteropathy-associated T-cell lymphoma
ENKL	extranodal NK/T-cell lymphoma, nasal type
EZH	enhancer of zeste homolog
EZH1/2	enhancer of zeste homolog 1 and 2
FTCL	follicular T-cell lymphoma
GGT	gamma-glutamyltransferase
H3K27	histone H3 lysin 27
HSTL	hepatosplenic T-cell lymphoma
Initial Review Report	Review Report on Ezharmia Tablets 50 mg, Ezharmia Tablets 100 mg dated August 8, 2022
MedDRA	Medical Dictionary for Regulatory Activities
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
MEITL	monomorphic epitheliotropic intestinal T-cell lymphoma
NA	not assessable
NCCN guidelines	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, T-Cell Lymphomas
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NED	no evidence of disease
NHL	non-Hodgkin lymphoma
NK cells	natural killer cell
OS	overall survival
Partial change application	Application for partial changes
PCGDTCL	primary cutaneous gamma delta T cell lymphoma
PD	progressive disease
P-gp	P-glycoprotein
PK	pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	population pharmacokinetics
PR	partial response
PT	preferred terms
PTCL	peripheral T-cell lymphoma
PTCL-NOS	PTCL not otherwise specified
PTCL-TFH	nodal PTCL with T follicular helper cells
QD	quaque die

SD	stable disease
SOC	system organ class
SPTCL	subcutaneous panniculitis-like T-cell lymphoma
Study J101	Study DS3201-A-J101
Study J201	Study DS3201-A-J201
Study U202	Study DS3201-A-U202
Valemetostat	Valemetostat Tosilate